does not believe that it can find that "testing is necessary" as would be a prerequisite for mandating testing under section 4 of TSCA. Therefore, EPA has decided not to initiate a rule to require further environmental testing of acrylamide at this time. It is conceivable that the results of these tests being performed by Industry may raise concerns which might indicate a need to perform additional testing for chronic effects to aquatic organisms (e.g., if the tests show acrylamide to be highly toxic). EPA will evaluate the need for additional testing when these results are available. If these or other new data reveal a need for further testing which Industry is unwilling to conduct, the Agency can require it through a section 4 test rule at that time.

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V. Public Record

EPA has established a public record for this decision not to pursue testing under section 4, docket number OPTS-47003B, which is available for inspection from 8:00 a.m. to 4:00 p.m. Monday through Friday, excluding legal holidays, in Rm. E-107, 401 M St., SW., Washington, D.C. 20460. This record includes basic information considered by the Agency in developing this decision. This record includes the following information:

1. Federal Register notice containing the designation of acrylamide to the Priority List and any comments on acrylamide in response to that notice.

2. Federal Register notice containing the Agency's response to the ITC recommendation that acrylamide be considered for health effects testing under TSCA section 4(a).

3. Communications: (a) Public and inter-agency communications, including memoranda, comments and proposals.

(b) Contact reports of telephone conversations.

(c) Meetings.

4. Industry submitted protocols and testing schedules.

(Sec. 4, 90 Stat. 2003; (15 U.S.C. 20001)

Dated: December 27, 1982.

John W. Hernandez,

Acting Administrator.

[FR Doc. 83-328 Filed 1-3-83; 8:45 am]

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[OPTS-42029; TSH-FRL No. 2246-7]

Isophorone; Response to the Interagency Testing Committee

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice.

SUMMARY: This notice is EPA's response to the Interagency Testing Committee's (ITC's) recommendation that isophorone be tested for health effects under section 4(a) of the Toxic Substances Control Act (TSCA). Following publication of the ITC report, the National Toxicology Program initiated a long-term bioassay of isophorone. In addition, the major U.S. manufacturers of isophorone have proposed to carry out mutagenicity and teratogenicity tests of isophorone. EPA believes that, together, these testing programs adequately respond to all of the ITC recommendations other than that for an epidemiology study. The Agency believes that requiring such a study is not warranted at this time. Consequently, the EPA is not, at this time, initiating rulemaking under section 4(a) to require health effects testing of isophorone. EPA seeks comments on its conclusions and on the adequacy of the proposed industry testing program.

DATE: Comments should be submitted on or before February 22, 1983.

ADDRESS: Written comments should bear the document control number OPTS-42029 and should be submitted in triplicate to: TSCA Public Information Office (TS-793), Office of Pesticides and Toxic Substances, Environmental Protection Agency, Rm. E-108, 401 M St., SW., Washington, D.C., 20460.

The administrative record supporting this action is available for public inspection in Rm. E-107 at the above address from 8:00 a.m. to 4:00 P.M.,

Monday through Friday, except legal holidays.

FOR FURTHER INFORMATION CONTACT: Douglas G. Bannerman, Acting Director, Industry Assistance Office (TS-799), Office of Toxic Substances, Environmental Protection Agency, Rm. E-511, 401 M St., SW., Washington, D.C. 20460. Toll Free: (800-424-9065), In Washington, D.C.: (554-1404), Outside the USA: (Operator 202-554-1404).

SUPPLEMENTARY INFORMATION:

I. Introduction

Section 4(a) (Pub. L. 94-467, 90 Stat. 2006; 15 U.S.C. 2601 *et seq.*) of the Toxic Substances Control Act (TSCA) authorizes the EPA to promulgate regulations requiring testing of chemical substances and mixtures in order to develop data relevant to determining the risks that such chemicals may present to health and the environment. Section 4(e) of TSCA established an Interagency Testing Committee (ITC) to recommend to the EPA a list of chemicals to be considered for promulgation of testing rules under section 4(a) of the Act.

The ITC placed isophorone on its priority testing list, as published in the Federal Register of June 1, 1979, (44 FR 31867). It recommended that isophorone be considered for testing for carciongenicity, mutagenicity, teratogenicity, and other chronic effects and that an epidemiology study be performed. The ITC recommended that isophorone be considered for carcinogenicity testing because of the large number of workers believed to be exposed to isophorone, its chemical structure, which suggests that isophorone has the potential to act as a direct alkylating agent, and because of the lack of carcinogenicity test data. The possible alkylating activity of isophorone and the lack of adequate test data were the reasons cited by the ITC in recommending mutagenicity testing. The ITC recommended that isophorone be considered for teratogenicity testing because no information was available on potential teratogenic effects. The ITC recommended that chronic effects testing be performed on isophorone because of its high exposure potential and the lack of information on its chronic toxicity. Finally, the ITC recommended that an epidemiology study be conducted due to the lack of information on chronic effects in humans from occupational exposure to low levels of isophorone. This notice provides EPA's response to the ITC's designation of isophorone for testing, as required by TSCA section 4(e).

II. Assessment of Exposure and Health Effects

Isophorone is an alpha, beta-unsaturated ketone with relatively low volatility. Its vapor pressure is 0.38 mm Hg at 20°C (Ref. 5). Its molecular formula is $C_9H_{14}O$.

The known chemical and physical data on isophorone include water solubility of 12,000 mg/l at 20°C (Ref. 5), an estimated octanol/water partition coefficient of 2.26 (Ref. 9), vapor density of 4.77 (Ref. 10) and a boiling point of 213-214°C (Ref. 11).

Isophorone is used chiefly as a solvent in the formulation of lacquers, and other surface coatings (Ref. 1). It is used in solvent mixtures for finishes, for polyvinyl and nitrocellulose resins, pesticides, and stoving lacquers (Ref. 4). Isophorone is an excellent solvent for many oils, fats, gums, and resins, and because of its chemical structure it is also used as a chemical intermediate for alcohols, and for synthesis of 3,5-dimethyl-aniline (Refs. 4, 11-13).

It is estimated that isophorone production is 20-30 million pounds per year and is decreasing because of its replacement, in some uses, with less costly compounds. Domestic sales account for 22-27 million pounds per year; exports, for 4-9 million pounds per year (Ref. 1). An estimated one million pounds were imported from the United Kingdom in 1981 (Ref. 2).

The National Institute for Occupational Safety and Health (NIOSH) estimated that 1,507,000 workers are potentially exposed to isophorone (Ref. 6). The CMA Ketones Panel believes NIOSH greatly overestimated exposure and that a more accurate estimate of exposure is 15,000-45,000 workers (Ref. 1). This estimate is still considered by EPA to indicate that a substantial number of workers may be exposed to isophorone. A recent study of worker exposure in a screen printing plant showed that workers were exposed to isophorone vapors in eight-hour time weighted average concentrations up to 23 parts per million (ppm) (Ref. 19). This is nearly five times the threshold limit value (TLV) for workplace exposure of five ppm (Ref. 17). NIOSH has recommended that this limit be reduced to four ppm as a result of a report that fatigue followed worker exposure to isophorone at levels of 5-8 ppm (Ref. 14). There does not appear to be any significant consumer exposure to isophorone covered by TSCA; however, isophorone may be present as an impurity in the drug clofibrate used to treat hyperlipidemia in humans and in some pesticides and plant growth retardants (Ref. 16).

Isophorone has been found in drinking water in Cincinnati, Ohio, at a level of 0.02 parts per billion (ppb) (Ref. 7), and in New Orleans, Louisiana, at 1.5-2 ppb (Ref. 24). It was also found at trace levels (less than 0.01 ppb) in water samples from the Delaware River (Ref. 23), and in wastewater from tire manufacturing, latex processing and chemical plants (Ref. 8).

In light of existing toxicity data on isophorone, the Agency does not expect isophorone to pose a significant health hazard at such low levels to the populations utilizing the drinking water supplies, nor accumulate in levels which result in significant environmental contamination.

Human case reports and studies indicate that isophorone is an eye and nose irritant (Ref. 15). Studies in animals exposed by inhalation, ocular and dermal routes also demonstrate that isophorone is an irritant. The oral LD_{50} for isophorone is reported to be 2,150 to 2,370 mg/kg in rats and 2,000 mg/kg in mice (Ref. 18).

Rats that died from inhalation exposure (1,800 ppm for 4 hours) exhibited the following gross pathologic changes: petechia and massive hemorrage of the lungs, congestion of stomach and liver, excess peritoneal fluid, a pale brownish color of the kidneys and orange-tinted spleens (Ref. 3).

No chronic or subchronic studies were found in the literature; however, the National Cancer Institute is currently performing a 2-year chronic bioassay for isophorone. The results are expected to be available by January, 1983. The range-finding subchronic study in Fisher 344 rats and B6C3F1 mice showed no gross pathology and no histopathologic lesions related to compound administration. Dosing was oral gavage at 62.5, 125, 250, 500 and 1,000 mg/kg/day for 90 days (Ref. 21).

The National Toxicology Program of the National Institutes of Health tested isophorone in the Ames assay. Four strains of bacteria were used with and without activation. All results were negative (Ref. 22).

EPA is aware of no data from teratogenicity testing of isophorone and of no epidemiology studies of persons exposed to isophorone.

III. Proposed Testing

The Ketones Program Panel and the Agency began discussion in 1981 regarding testing needs for isophorone. The Panel has submitted protocols for mutagenicity and teratology testing of isophorone (Ref. 20).

The Panel has proposed the following mutagenicity studies: a mouse lymphoma mutagenicity assay, an unscheduled DNA synthesis test, and a micronucleus test. The results of the mouse lymphoma and unscheduled DNA synthesis tests will permit an assessment of the potential of isphorone to cause gene mutations. The mouse lymphoma test will permit the evaluation of the mutagenic potential of isophorone by measuring the ability of isophorone to cause mutation at the thymidine kinase locus in the L5178 TK+/− mouse lymphoma cell line. The unscheduled DNA synthesis test will measure the ability of isophorone to induce genetic damage which will trigger DNA repair. The micronucleus tests, an *in vivo* cytogenetics test, is a test for the potential to induce chromosomal damage either through chromosomal breakage or interference with normal mitotic cell division.

The Panel also has proposed an inhalation teratology study for isophorone in two species (rat and mouse) using three dose levels, including a negative control. Standard experimental design procedures for teratology testing are proposed, including exposure during days 6–15 of the gestation period.

The Panel has agreed to adhere to the FDA Good Laboratory Practice Standards (43 FR 59986, Dec. 22, 1978), and has agreed to furnish EPA with names and addresses of laboratories conducting the tests described above as soon as they are available. The specific tests being performed by each laboratory shall be indicated.

The Panel has also agreed to permit laboratory audits/inspections at the request of authorized representatives of the EPA in accordance with the authority and procedures outlined in TSCA section 11. These inspections may be conducted for purposes which include verification that testing has begun, that schedules are being met, that reports accurately reflect the underlying raw data and interpretations and evaluations thereof, and that the studies are being conducted according to the FDA Good Laboratory Practice Standards cited above.

Finally, the Panel has agreed that all raw data, documentation, records, protocols, specimens, and reports generated as a result of a study will be retained as specified in the FDA Good Laboratory Practice Standards cited above and made available during an inspection or submitted to EPA if required by EPA or its authorized representative.

The Agency plans to publish quarterly in the **Federal Register** a notice of the receipt of any test data submitted under this agreement. Subject to TSCA section 14, the notice will provide information similar to that described in TSCA section 4(d). Except as otherwise provided in TSCA section 14, such data will be made available by the EPA for examination by any person. The Panel understands that TSCA section 14(b)(1)(A) governs Agency disclosure of all test data submitted pursuant to section 4 of TSCA.

Finally, the Panel understands that failure to conduct the testing according to the test protocols agreed upon by the Panel and EPA or failure to follow Good Laboratory Practices may invalidate the tests. In such cases, a data gap may still exist, and the Agency may decide to promulgate a test rule or otherwise require further testing.

The Panel agreed to begin the teratology study within three months of publication of the final notice with final report submission within 12 months of study initiation. Mutagenicity testing would begin approximately one month after publication of the final notice with completion expected six months after initiation. Should the Panel fail to make a good faith effort to adhere to its testing schedule outlined above, EPA will initiate rulemaking to require testing.

IV. Decision Not To Initiate Rulemaking

When combined with the work ongoing at National Cancer Institute, EPA believes that the industry's proposed testing program will provide an adequate basis to evaluate the effects of concern to the ITC. Should information developed through this testing program or otherwise reveal a need for additional testing that industry is unwilling to perform, the Agency reserves the right to proceed with rulemaking under section 4(a). EPA's specific responses to the various recommendations of the ITC are set forth below.

1. *Carcinogenicity and Chronic Effects.* The National Cancer Institute (NCI) is currently performing a chronic bioassay that includes carcinogenicity testing for isophorone. The NCI chronic bioassay on isophorone is expected to provide sufficient data to reasonably predict or determine the potential of isophorone with respect to oncogenicity and chronic endpoints. In addition, the range-finding subchronic study showed no gross pathology or histopathologic lesions related to compound administration.

NCI is administering isophorone by oral gavage in its bioassays; however, the major route of human exposure is inhalation. EPA has considered the desirability of performing some basic toxicokinetic studies (compound uptake, distribution and elimination) using the route of administration used in testing (gavage) and the route of administration which mimics human exposure (inhalation) to provide a better basis for evaluating the NCI test data. EPA will consider toxicokinetics studies if they appear warranted based on the outcome of the NCI studies. The need for such data might be more acute if the NCI study shows significant effects. The Agency is requesting comments on the criteria under which toxicokinetic studies should be required.

2. *Mutagenicity.* The Panel has submitted protocols for three mutagenicity tests: a mouse lymphoma mutagenicity assay; an unscheduled DNA synthesis test; and a micronucleus test. Although the micronucleus test protocol is inconsistent with the TSCA and OECD test guidelines, EPA is working with the Panel to resolve these differences. Assuming successful resolution of this issue and no unresolvable issues are identified by commentors, the Agency will accept these protocols as satisfying the basic gene mutation and chromosomal aberration testing needs; therefore, additional mutagenicity testing is not being required at this time. If these studies indicate genotoxic potential, EPA will pursue further mutagenicity testing, either through negotiations or by rule.

3. *Teratology.* The Panel has submitted a protocol for an inhalation teratology study on isophorone which is expected to provide adequate data for determining teratogenic potential. Thus, there is no need to initiate rulemaking at this time to require teratogenicity studies.

4. *Epidemiology.* Because there are no documentable health hazards reported for isophorone, the Agency does not believe that it should require epidemiologic studies at this time. Should the NCI or CMA testing programs for isophorone identify such a hazard, EPA will reconsider the need for requiring an epidemiology study.

V. References

(1) Report of the Chemical Manufacturers Association, Ketones Program Panel. October 21, 1981. Exhibit 2.

(2) BOC-Imports. 1979–1982. Bureau of Census. As referenced in the draft Level I Economic Evaluation: Isophorone, by Mathtech, Inc. under Contract 68–01–6287 for EPA. p. 22.

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(15) Silverman L, Schulte HF, First MW. 1946. Further studies on sensory response to certain industrial solvent vapors. J. Ind. Hyg. Toxicol. 28:262–266.

(16) Johansson E, Ryhage R. 1976. Gas chromatographic-mass spectrometric identification and determination of residual by-products in clofibrate preparations.

(17) American Conference of Governmental Industrial Hygienists. 1980. Threshold Limit Values for Chemical Substances in Workroom Air Adopted by ACGIH for 1980. ISBN: 0–936712–29–5.

(18) Bukhalovskii AA, Shugaev BB. 1976. Toxicity and hygienic standardization of isophorone, dihydroisophorone, and dimethylphenyl carbinol. Prom. St. Sint. Kauch. 76(2):4–5.

(19) Samini B. 1982. Exposure to isophorone and other organic solvents in a silk screen printing plant. American Industrial Hygiene Association Journal. Jan. 1, 1982; 43:43–48.

(20) Chemical Manufacturers Association. 1982. Ketones Program Panel. Proposed voluntary test program on isophorone. Dated October 8, 1982.

(21) National Toxicology Program. 1979. Prechronic test review. Contract No. 600259. Papanicalou Cancer Research Center, Miami, Florida.

(22) National Toxicology Program. 1982. Mutagenesis testing results. *NTP Technical Bulletin, Issue 6, p. 6.*

(23) Sheldon LS, R.A. Hites. 1978. Organic compounds in Delaware River. Environ. Sci. Technol. 12:1188.

(24) Shackelford WM, L. H. Keith. 1976. Frequency of organic compounds identified in water. U.S. EPA. 600/4–76–062. Athens, Georgia, p. 626.

VI. Public Record

The EPA has established a public record for this testing decision (Docket Number OPTS–42029). This record includes:

(1) **Federal Register** notice containing the designation of isophorone to the priority list and all comments on isophorone received in response to that notice.

(2) Communications with industry.

(3) Letters.

(4) Contact reports of telephone conversations.

(5) Meeting summaries of Agency-industry and Agency-public meetings.

(6) Testing proposal.

(7) Published and unpublished data.

(8) **Federal Register** notice requesting comment on the negotiated testing proposal and all comments received in response to that notice.

This record, containing the basic information considered by the Agency in developing the decision, is available for inspection in the OPTS Reading Room 8:00 a.m. to 4:00 p.m., Monday through Friday (except legal holidays) in Room E–107, 401 M Street, SW., Washington, D.C. 20460. The Agency will supplement this record periodically with additional relevant information received.

(Sec. 4, 90 Stat. 2003 (15 U.S.C. 2061))

Dated: December 20, 1982.

Anne M. Gorsuch,

Administrator.

[FR Doc. 83–327 Filed 1–3–83; 3:55 pm]

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